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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,553	11/30/2004	Tadaaki Yabubayashi	09853/0202140-US0	7061

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EXAMINER	
POHNERT, STEVEN C	
ART UNIT	**PAPER NUMBER**
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No. 10/516,553	Applicant(s) YABUBAYASHI ET AL.	
	Examiner Steven C. Pohnert	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 22 January 2007.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-22 is/are pending in the application.

4a) Of the above claim(s) 15-22 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-14 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 11/30/2004 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 11/30/2004, 2/21/2007.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-14 in the reply filed on 1/22/2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 15-22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1/22/2007.

The requirement is still deemed proper and is therefore made FINAL.

An office action on the merits of claims 1-14 follows.

Information Disclosure Statement

2. The information disclosure statement filed 2/21/2007 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered.

The prior art lined through was not considered because they lack an English translation. The prior art marked with ABS had an English abstract which was considered.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-14 recite, "detecting/discriminating". It is unclear if the applicant is detecting the complex that are formed or discriminating the formed complex.

Claim 6 recites the limitation "the label modification operation" in 4th line. Claim 6 is multiply dependent on claims 1-4. Claim 1 does not recite or require modifying a label. There is insufficient antecedent basis for this limitation in the claim. Further claims 2-4 recite "modifying with a label", which is not "the label modification operation."

Claim 10 is indefinite as it recites, "(including Si)". It is unclear if the "(including Si)" is a limitation of the claim.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1, 3, 5, 6, 8-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Cass et al (US Patent 6,312,906 issued November 6, 2001).

With regards to claim 1, Cass et al teaches a method of detecting a biochemical sample by use of hairpin structure attached to a solid phase (see abstract and figure 1). Cass exemplifies this method in example 1(see column 16, lines 10-26). Cass teaches the attachment of a oligonucleotide probe with an internal hairpin (or loop) with a biotin derivative and attaching the probe to a platinum surface (electrode) (see column16, lines 12-15). Cass et al further teaches the use of an electrode (see column 15, line 50). Cass further teaches a solution of target nucleic acids containing a sequence complementary to a sequence in the hairpin loop of the probe results the movement of the fluorescent moiety away from the surface and an increase in intensity (see column 16 lines 20-26). Cass thus teaches a method of detecting a biochemical reactant by hybridizing the specimen to a nucleic acid probe with a loop structure on a biochip with an electrode and detecting the duplex nucleic acid complex formed.

Claim 3, in the event that "label" is broadly interpreted to mean only any detectable substance, the target nucleic itself is labeled with nucleotides. Cass teaches the probe is bound by a test sample that has a label (nucleic acid extension beyond that bound by the probe) (see figure 2). These claims are not limited to fluorophores or radioisotopes.

With regards to claims 5 and 6, Cass et al teaches, " the quenching of the fluorescein fluorescence signal thus relieved and the intensity of the fluorescent signal increases" (column 16, lines 37-39). As Cass teaches that hybridization results in an increase in the fluorescent signal, he inherently teaches the detection before and after each step, as well as the comparison on the initial and final fluorescence.

With regards to claim 8 and 9, Cass teaches in the first step the internal hairpin is synthesized with a biotin derivative (1^{st} label) (see column 16, lines11-12). Cass teaches in the second step that streptavidin (2^{nd} label) is immobilized onto a platinum surface (see column 16, lines 12-14). Cass teaches a third step the biotin labeled hairpin is added to the platinum surface and followed by the immobilization streptavidin in the final step (targeting the 1^{st} label with a second label)(see column 16, lines 15-20). Cass et al thus teaches a multi-stage modification in which a second label (streptavidin) is attached to a first label (biotin).

With regards to claim 10, Cass teaches the use of fluorescein (see column 16, line 24). Fluorescein is a fluorescent label or dye. Cass thus teaches a method of detecting a biochemical wherein the label is a fluorescent dye or fluorescent label.

7. Claims 1-4, 5, 6, 8-10 rejected under 35 U.S.C. 102(b) as being anticipated by Gold et al (WO/1999/31275, Published June 24, 1999).

With regards to claims 1and 2, Gold et al teach teaches the use of mutually complementary nucleic acids for detection of binding of a target molecule to a nucleic acid ligand (see page 20, lines 26-30). Gold teaches the detection of ligand binding by electronic means (see abstract) and further teaches the use of gold or silver as the substrate for the array (see page 12, line 30). Thus the gold or silver of Gold allow for detection by the transfer of electrons and thus are electrodes (see page 26, lines 7-31). Gold further teaches, " an insulative silica "gate" is placed between two n-type semiconductors, forming a biochip. Current will flow from one semiconductor to the other when a conducting channel is formed in the gate and a potential difference is

applied" (see page 26, lines 9-14). Gold et al teaches a target molecule is a nucleic acid (see page 6, lines 11-15). Gold further teaches that upon targeting molecule binding to the nucleic acid ligand a conformation change occurs that allows hybridization of further nucleic acid molecules to the nucleic acid ligand (page 20, lines 28-30). Gold teaches the nucleic acid molecules further modifying the nucleic acid ligand also undergo a conformational change allowing the formation of an intermolecular hybridization complex to form (see page 20, line 30-page 21, line 5). Gold further teaches the mutually complementary nucleic acids are stem-loop nucleic acids (see page 21, lines 15-16). Gold further teaches that scaling up of technology accurately allows the measurement of thousands of discrete changes in current drain (see page 26, line 23).

With regards to claims 3 and 4, Gold teaches the use of nucleic acids with a fix sequence surrounding a randomized region. These fixed regions are labels.

With regards to claim 5 and 6, Gold teaches binding of the target molecule results in a net loss or gain of ions at that region of the chip, altering conductance and a current drain in this area of the chip (see page 26, lines 16-22). Gold's teaching of detecting alterations in current conductance after the addition of a target ligand inherently requires that the conductance before addition of the ligand is known. Gold thus teaches the detection and quantification before and after hybridization.

With regards to claims 8 and 9, Gold teaches the thiolpropionate having a photochemical reactive group is couple to functional groups on the surface of the biochip (see page 13, lines 8-10). Gold further teaches light of the appropriate

wavelength, followed by the attachment to substrate (see page 13, lines 10-16) and the unbound nucleic acid is washed away. Gold further teaches the use of photoactivatable biotin (label) by a similar method (see page 13, lines 23-25).

With regards do claim 10, Gold teaches labeling with fluorescent labels (see page 14, line 31).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claim 3, 7, 11, 12, 13, 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cass et al (US Patent 6,312,906 issued November 6, 2001) in view of Blackburn et al (US Patent 6264825 issued July 24, 2001).

Claim 3 is being rejected as being required to have a non-nucleic acid label.

Cass et al teaches a method of detecting a biochemical sample by use of hairpin structure attached to a solid phase (see abstract and figure 1). Cass exemplifies this method in example 1(see column 16, lines 10-26). Cass teaches the attachment of a oligonucleotide probe with an internal hairpin (or loop) with a biotin derivative and attaching the probe to a platinum surface (electrode) (see column16, lines 12-15). Cass further teaches a solution of target nucleic acids containing a sequence complementary to a sequence in the hairpin loop of the probe results the movement of the fluorescent moiety away from the surface and an increase in intensity (see column 16 lines 20-26).

Cass thus teaches a method of detecting a biochemical reactant by hybridizing the specimen to a nucleic acid probe with a loop structure on a biochip with an electrode and detecting the duplex nucleic acid complex formed.

Cass does not teach the labeling of a biochemical sample in advance of hybridization (claims 3). Cass et al does not detection of the probes on each electrode prior to the hybridization with the biochemical reactant (claim 7). Cass et al does not teach detection of complex by electronic methods (claim 11). Cass et al does not teach detection/discrimination of the complex by electronic and magnetic methods (claim 12). Cass et al does not teach detection by electronic and optical methods (claim13). Cass et al does not teach detection by magnetic, optical and electronic means (claim 14).

However, Blackburn et al teaches a method of detecting an analyte by electron transfer moiety (ETM) (see abstract). Balckburn et al teaches the detection of the use of a plurality of gold electrodes (see column 2, lines 60-65). Blackburn further teaches the detection of probes prior to any experiment for use as an internal control for calibration of an experiment (see column 48, lines 4-14) (claim 7). Blackburn teaches the enzymatic incorporation of an ETM (label) during PCR (see column 60, lines 8-11) (claim 3, biochemical probe modified in advance). Blackburn et al further teaches the detection of the presence of ETM on the surface of the electrodes by amperommetry, voltametry, capacitance or impedance (see column 81, lines 55-67) (claim 11).

With regards to claim 12, Blackburn teaches the use of magnetic particles can be used to associate the ligand complex with the detection electrode, thus allowing detection/discrimination comprising magnetic and electronic methods (see column, 19,

lines 33-39). Thus Blackburn's use of magnetic particles to selectively move the ligand complex to the electrodes where it is detected results in detection based on discrimination (movement on magnetic particles) and detection by electronic means at electrode.

With regards to claim 13, Blackburn teaches detection of the presence of the ETM on the surface of the detection electrode by use of electrochemiluminescence (see column 80, line 47). Electrochemiluminesence is activation of chemilumensence by a current. Thus the increase in the current results in detection of an optical signal.

With regards to claim 14, Blackburn teaches the use of magnetic particles used to associate the ligand complex with the detection electrode, thus allowing detection/discrimination comprising magnetic and electronic methods (see column, 19, lines 33-39). Further, Blackburn teaches detection of the presence of the ETM on the surface of the detection electrode by use of electrochemiluminescence (see column 80, line 47). Electrochemiluminesence is activation of chemilumensence by a current. Thus the increase in the current results in detection of an optical signal. Thus Blackburn teaches the detection/discrimination of a chemical reactant complex comprising the use of discriminating on magnetic signal, current values and optical.

Therefore it would have been prima facie obvious to one of ordinary skill in art at the time the invention was made to combine the hairpin probes of Cass with the diction method of Blackburn. The skilled artisan would be motivated because Blackburn teaches his method allows concentration of the target ligand with the capture ligand maximizing interaction (see column 9, lines 37-40). The ordinary artisan would further

be motivated as this allows very small samples to be analyzed (see column 81, lines 25-27). The ordinary artisan would be motivated to use Blackburn's method of internal control as it allows more accurate and quantitative detection. Thus the combined teachings of Cass and Blackburn would result in the ability to increase the sensitivity of the loop probes of Cass by concentrating the biochemical samples with the probes. The combined teachings would also allow for improved sensitivity because the quantization of the probes would result in a better determination of the limits of detection of the assay.

10. Claims 4, 7, 11, 12, 13, 14 are ejected under 35 U.S.C. 103(a) as being unpatentable over Gold et al (WO/1999/31275, Published June 24, 1999) in view of Blackburn et al (US Patent 6264825 issued July 24, 2001).

Claim 4 is being rejected as being required to have a non-nucleic acid label.

Gold et al teach teaches the use of mutually complementary nucleic acids for detection of binding of a target molecule to a nucleic acid ligand (see page 20, lines 26-30). Gold teaches the detection of ligand binding by electronic means (see abstract) and further teaches the use of gold or silver as the substrate for the array (see page 12, line 30). Thus the gold or silver of Gold allow for detection by the transfer of electrons and thus are electrodes (see page 26, lines 7-31). Gold further teaches, " an insulative silica "gate" is placed between two n-type semiconductors, forming a biochip. Current will flow from one semiconductor to the other when a conducting channel is formed in the gate and a potential difference is applied" (see page 26, lines 9-14). Gold et al teaches a target molecule is a nucleic acid (see page 6, lines 11-15). Gold further

teaches that upon targeting molecule binding to the nucleic acid ligand a conformation change occurs that allows hybridization of further nucleic acid molecules to the nucleic acid ligand (page 20, lines 28-30). Gold teaches the nucleic acid molecules further modifying the nucleic acid ligand also undergo a conformational change allowing the formation of an intermolecular hybridization complex to form (see page 20, line 30-page 21, line 5). Gold further teaches the mutually complementary nucleic acids are stem-loop nucleic acids (see page 21, lines 15-16). Gold further teaches that scaling up of technology accurately allows the measurement of thousands of discrete changes in current drain (see page 26, line 23).

Gold does not teach the labeling of a biochemical sample in advance of hybridization (claims 3). Gold et al does not detection of the probes on each electrode prior to the hybridization with the biochemical reactant (claim 7). Gold et al does not teach detection of complex by electronic methods (claim 11). Gold et al does not teach detection/discrimination of the complex by electronic and magnetic methods (claim 12). Gold et al does not teach detection by electronic and optical methods (claim13). Gold et al does not teach detection by magnetic, optical and electronic means (claim 14).

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(claim 3 and 4, biochemical probe modified in advance). Blackburn et al further teaches the detection of the presence of ETM on the surface of the electrodes by amperommetry, voltametry, capacitance or impedance (see column 81, lines 55-67) (claim 11).

With regards to claim 12, Blackburn teaches the use of magnetic particles can be used to associate the ligand complex with the detection electrode, thus allowing detection/discrimination comprising magnetic and electronic methods (see column, 19, lines 33-39). Thus Blackburn's use of magnetic particles to selectively move the ligand complex to the electrodes where it is detected results in detection based on discrimination (movement on magnetic particles) and detection by electronic means at electrode.

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teaches the detection/discrimination of a chemical reactant complex comprising the use of discriminating on magnetic signal, current values and optical.

Therefore it would have been prima facie obvious to one of ordinary skill in art at the time the invention was made to combine the hairpin probes of Gold with detection method of Blackburn. The skilled artisan would be motivated because Blackburn teaches his method allows concentration of the target ligand with the capture ligand maximizing interaction (see column 9, lines 37-40). The ordinary artisan would further be motivated as this allows very small samples to be analyzed (see column 81, lines 25-27). The ordinary artisan would be motivated to use Blackburn's method of internal control as it allows more accurate and quantitative detection. Thus the combined teachings of Gold and Blackburn would result in the ability to increase the sensitivity of the loop probes of Blackburn by concentrating the biochemical samples with the probes. The combined teachings would also allow for improved sensitivity because the quantization of the probes would result in a better determination of the limits of detection of the assay.

Summary

No claims are allowed over prior art cited.

Conclusions

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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3/20/07